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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,256	05/05/2006	Maria T. Abreu	025663-001310US	7450

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,256	ABREU ET AL.	
	Examiner	Art Unit	
	JEANINE A. GOLDBERG	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *05 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed May 5, 2006.

2. Currently, claims 1-23 are pending.

Priority

3. This application is a 371 of PCT/US03/23926, filed July 30, 2003 and claims priority to 10/356736, filed January 30, 2003 and provisional application 60/407,391, filed August 30, 2002.

Drawings

4. The drawings are acceptable.

Claim Rejections - 35 USC § 112-Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-23 are drawn to a method of diagnosing or predicting susceptibility to a clinical subtype of Crohn's disease characterized by fibrostenosing disease by

determining the presence or absence of a fibrostenosis-predisposing allele linked to NOD2/CARD15 to detect fibrostenosing disease.

The specification teaches that in an analysis in a combined cohort representing cohort 1 and 2 the frameshift mutation 3020insC demonstrated the greatest association with fibrostenosing disease (p=0.006).

There is not adequate description of the genus of a fibrostenosis-predisposing allele linked to CARD15/NOD2. The specification only discloses a single variant within the scope of the genus: a fibrostenosis-predisposing allele linked to CARD15/NOD2. The general knowledge in the art concerning variants in linked with the frameshft mutation 3020incC does not provide any indication of how to readily identify these variants. The single variant described is not representative of the genus of a fibrostenosis-predisposing allele linked to CARD15/NOD2. There is substantial variability among the species of nucleic acids encompassed in the scope of the claim because only one specific mutation has been identified in the very large gene. The specification has also not defined a structural feature of the variants which would be common to all members of the genus that constitutes a substantial portion of the genus. Furthermore, one of skill in the art would conclude that applicant was not in possession of the claimed "a fibrostenosis-predisposing allele linked to CARD15/NOD2" because the description of only one member of this genus is not representative of the variants of the genus and is insufficient to support the claims. Thus, the specification does not adequately provide a written description for a fibrostenosis-predisposing allele linked to CARD15/NOD2.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and breadth of claims

Claims 1-23 are drawn to a method of diagnosing or predicting susceptibility to a clinical subtype of Crohn's disease characterized by fibrostenosing disease by determining the presence or absence of a fibrostenosis-predisposing allele linked to

NOD2/CARD15 to detect fibrostenosing disease. Claim 7 are specifically directed to SNP8, 12, and 13. Claim 10 is drawn to markers JW1, 15, 16, 17, and 18.

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The unpredictability of the art and the state of the prior art

The art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

The art teaches that presence of SNPs in the same gene does not indicate that each of the genes is associated with the same diseases. Meyer et al. (PG Pub 2003/0092019), for example, teaches that SNPs in the CADPKL gene are not each associated with neuropsychiatric disorders such as schizophrenia. Specifically Meyer teaches that cadpkl5 and cadpkl6 are not associated with the disease, however cadpkl7 has a p-value of less than 0.05, therefore an association exists. Each of these

polymorphisms are SNPs within the CADPKL gene, however, it is apparent that they are not all associated in the same manner with disease. Thus, Meyer exemplifies that the association of a single SNP in a gene does not indicate that all SNPs within the gene are associated with the disease.

Additionally, Ioannidis (Nature Genetics, Vol. 29, pages 306-309, November 2001) teaches that the results of the first study correlate only modestly with subsequent research on the same association (abstract). Ioannidis teaches that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract).

The art teaches p-values are used to assess whether studies are "real" or "pure chance". Thisted (May 1998) discuss what a p-value is. Thisted states that the p-value is important to determining whether differences observed are "real". Thisted states that "it has become scientific convention to say that p-values exceeding 0.05 (one in twenty) just aren't strong enough to be the sole evidence that two treatments being studied really differ in their affects" (page 5). Therefore, it is clear that significance in the form of a p-value helps to determine whether the analysis was due to chance alone or demonstrates a difference between two groups.

Ahmad et al. teaches the molecular classification of the clinical manifestations of Crohn's disease. 1007fsincC appears to have a statistically significant association of $p<0.0001$. 908Arg appears to have a statistical significant association with $p<0.001$. Ahmad teaches stenotic disease was positively associated with the presence of a NOD2/CARD15 mutation, but this was not independent of the link with ileal disease. No other independent associations were found with disease behavior phenotypes (page 864, col. 1).

Lakatos et al. (Orv. Hetil. Vol. 145, No. 27, pages 1403-1411, July 2004) teaches NOD2/CARD15 mutations and genotype-phenotype correlations in patients with Crohn's disease in a Hungarian population. Lakatos teaches that G908R mutation was uncommon in Hungarian Crohn's pateitns. The presence of the mutation was associated with ileal but not fibrostenosing disease (abstract). While the numbering system differs, it appears that Lakatos G908R mutation is the same mutation as the instant specifications R675W (SNP8).

Kugathasan et al. (Gastroenterology, Vol. 126, No. 4, Supp. 2, pp A68, 524) teaches L1007FsinsC variant of CARD15/NOD2 is strongly associated with early onset and fibrostenosing behavior in pediatric crohn's disease (CD). Kugathasan analyzes three SNPs within the CARD15/NOD2 gene. It is noted here also that the number scheme is different than the instant application. The L1007FsinsC variant appears to be instant SNP13. Kugathasan teaches that R702W and G908R may not play a major role in pediatric onset CD.

Vavassori et al. (Inflamm Bowel Dis. Vol. 10, No. 2, pages 116-121, March 2004) teaches CARD15 mutation analysis in an Italian population. Vavassori teaches that Leu1007fsinsC but neither Arg702Trp nor Gly908Arg mutations are associated with Crohn's disease. Vavassori teaches classifying according to disease course into three groups including fibrostenosing (page 117, col. 2). Vavassori teaches a trend of association was seen between Leu1007fsinsC genotypes and either involvement of the distal ileum or fibrostenosing behavior. Vavassori teaches that the insC mutation was significantly associated with a fibrostenosing disease of the distal ileum. The insC homozygous genotype had an OR for firbrostenosing disease of the distal ileum of 11.1-fold (page 119, col.2). As illustrated in Table 5, the insC is stronger in homozygotes than in heterozygotes.

Guidance in the Specification and Working Examples

The specification analyzes relationship of NOD2/CARD15 rare variant alleles and clinical phenotypes of Crohn's disease in two cohorts. The claims are specifically drawn to diagnosing or predicting susceptibility to fibrostenosing disease. Genotyping and analysis was provided for three variant alleles stratified by phenotype. Results for the two cohorts was provided and reproduced below (see page 57, 59):

	R675W (SNP8)	G881R (SNP12)	3020insC (SNP13)
Cohort I	**P=0.389**	**P=0.458**	P=0.084
Cohort II	**P=0.315**	P=0.048*	P=0.018*

The specification teaches that in an analysis in a combined cohort representing cohort 1 and 2 the frameshift mutation 3020insC demonstrated the greatest association with fibrostenosing disease (p=0.006). As specifically provided by the data from tables on page 57 and 59, SNP8 and SNP12 do not appear to be predictably associated with fibrostenosing disease. The guidance provided by the specification amounts to an invitation for the skilled artisan to try and follow the disclosed instructions to make and use the claimed invention.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters which would have to be studied.

As provided in the art, associations between mutations and phenotypes is complex in nature. Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility. Ioannidis teaches

that both bias and genuine population diversity might explain why early association studies tend to overestimate the disease protection or predisposition conferred by a genetic polymorphism (abstract). Meyer exemplifies that the association of a single SNP in a gene does not indicate that all SNPs within the gene are associated with the disease. Therefore, given the teachings in the art, studies should be cautiously interpreted and analyzed. It is unpredictable that any mutation within a particular gene, namely NOD2/CARD15 or even a locus is associated with a particular phenotype, such as fibrostenosing disease, as required by the instant claims.

Additionally, the claims are broadly drawn to a "fibrostenosis-predisposing allele linked to a NOD2/CARD15 locus." This broad recitation encompasses SNPs, microsatellite markers, deletions, mutations, for example located within or outside the NOD2 gene. The specification provided three alleles, namely SNP8, SNP12, SNP13 It is clear from the data obtained in the instant application that each of these SNPs are not associated with fibrostenosis. It is unpredictable which alleles are associated with fibrostenosis. While the ordinary artisan may analyze additional alleles and mutations for an association with fibrostensis, the results of the analysis are unpredictable. Further, identifying additional alleles, either within NOD2 or linked to NOD2 would require undue experimentation without any guidance.

Claims 9-10 are directed to alleles JW1, JW15 and JW16. Claim 11-12 are directed to JW17 and JW18. The instant specification fails to analyze any associations between fibrostenosis and the alleles. As noted above, markers in the same gene do not predictably correlate with an association between the same phenotype.

The instant claims are drawn to SNP8, SNP12, SNP13. It is clear that the art identifies each of these SNPs using alternative numbering systems. Thus, it is unclear the location and context of the alleles within the NOD2 or CAD15 locus. Identifying the

location within a SEQ ID NO: would allow the skilled artisan to clearly understand which allele is being analyzed.

To practice the scope of the claims as broadly as drawn, would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, in a highly unpredictable art where the art specifically teaches difficulties in providing associations between markers and phenotypes. Further, the art and the specification provides insufficient guidance to overcome the art recognized difficulties for obtaining a statistically significant association between a marker and a phenotype. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the absence of a working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

7. Claims 1, 3, 4, 5, 6, 7, 8, 13-20 are rejected under 35 U.S.C. 102(a) as being anticipated by Ahmad et al. (Gastroenterology, Vol. 122, pages 854-866, April 2002).

Ahmad et al. teaches the molecular classification of the clinical manifestations of Crohn's disease. Ahmad teaches genotyping using PCR primers (limitations of Claim 19)Table 9 illustrate surgical stenotic disease and analyzes 1007fsincC; 908Arg and 702Trp. 1007fsincC appears to have a statistically significant association of $p<0.0001$. 908Arg appears to have a statistical significant association with $p<0.001$. Ahmad teaches stenotic disease was positively associated with the presence of a NOD2/CARD15 mutation, but this was not independent of the link with ileal disease. No other independent associations were found with disease behavior phenotypes (page 864, col. 1).

8. Claims 1, 3-8, 16-20 are rejected under 35 U.S.C. 102(a) as being anticipated by Abreu et al (Gastroenterology, Vol. 122, No. 4, Suppl. 1, ppA.29, 246).

It is noted that the authorship of the Abreu et al. reference is distinct from the inventorship of the instant application and that this rejection may be overcome by the filing of a 132 Katz-type declaration.

Abreu et al. teaches mutations in NOD2 are associated with fibrostenosing disease in patients with Crohn's disease (CD). The genotyping was performed for three rare alleles of the NOD2 gene, R675W, G881R, and 980fs by the Taqman MGB

system. Abreu teaches the frameshift mutation, 980fs demonstrated the greatest association with fibrostenosing disease (p for cohorts combined=0.009).

9. Claims 1, 3-8, 16-20 are rejected under 35 U.S.C. 102(a) as being anticipated by Radlmayr et al. (Gastroenterology, Vol. 122, No. 7, pages 2091-2095, June 2002).

Radlmayr et al. teaches the c-insertion mutation of the NOD2 gene is associated with fistulizing and fibrostenotic phenotypes in Crohn's disease. Radlmayr teaches patients with Crohn's disease were subdivided according to their respective phenotypes, e.g., fistulizing, fibrostenotic, or inflammatory by conventional clinical, endoscopic, radiologic, and histological criteria. When patients with Crohn's disease were stratified accoriding to the respective disease phenotype, the c-insertion mutation was associated with the fibrostenotic phenotype (p=0.023)(page 2091, col. 2). As seen in Table 1, the number of patients with or without the c-insertion allele according to the diseases were compared (page 2092, col. 1).

10. Claims 1, 3-8, 16-20 are rejected under 35 U.S.C. 102(a) as being anticipated Abreu et al. (Gastroenterology, Vol. 123, pages 679-688, August 29, 2002).

It is noted that the authorship of the Abreu et al. reference is distinct from the inventorship of the instant application and that this rejection may be overcome by the filing of a 132 Katz-type declaration.

Abreu teaches mutations in NOD2 are associated with fibrostenosing disease in patients with Crohn's disease. Abreu teaches two cohorts of consecutively identified

patients were genotypes for 3 single nucleotide variants of NOD2- R675W, G881R and 3020insC and phenotyped for disease behavior, disease location and serum immune markers. Abreu studies two distinct cohorts. In cohort 1, the clinical phenotype of fibrostenosing was stratified. Resuts for the two cohorts was provided and reproduced below:

	R675W (SNP8)	G881R (SNP12)	3020insC (SNP13)
Cohort I	P=0.389	P=0.458	P=0.084
Cohort II	P=0.315	P=0.048*	P=0.018*

Abreu teaches the findings are consistent with Lesage and Ahmad who described a genotype/phenotype association between NOD2 variants and fibrostenosing disease in 2 large series of European patients. Abreu further teaches that the Ahmad study did not find an association between NOD2 variants and fibrostenosing disease that was independent of an association with small-bowel disease (page 686, col. 1).

Conclusion

11. No claims allowable.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571) 272- 0745.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

/Jeanine A Goldberg/
Primary Examiner, Art Unit 1634
May 8, 2008